representing a perturbed state of said first biological system, said method comprising the steps of

(a) determining an error distribution statistic by fitting a reference pair of microarray experiments with an intensity independent statistic, wherein said reference pair of microarray experiments comprises a first reference microarray experiment, and a second reference microarray experiment that is a nominal repeat of said first reference microarray experiment;

(b) determining, for each paired differential microarray experiment in said plurality of paired differential microarray experiments, an amount of change in expression level of said cellular constituent between the second microarray experiment and the first microarray experiment of said paired differential microarray experiment using said error distribution statistic; and

(c) determining said probability that said expression level of said cellular constituent in said plurality of paired differential microarray experiments is altered by said perturbation by combining, for each paired differential microarray experiment in said plurality of paired differential microarray experiments, each amount of change in expression level of said cellular constituent determined in step (b) using a rank based method.

15. (Amended) A computer system for determining a probability that an expression level of a cellular constituent in a plurality of paired differential microarray experiments is altered by a perturbation, wherein each paired differential microarray experiment in said plurality of paired differential microarray experiments comprises a first microarray experiment representing a baseline state of a first biological system, and a second microarray experiment representing a perturbed state of said first biological system; the computer system comprising a processor, and a memory encoding one or more programs coupled to the processor and the one or more programs cause the processor to perform a method comprising the steps of

(a) determining an error distribution statistic by fitting a reference pair of microarray experiments with an intensity independent statistic, wherein said reference pair of microarray experiments comprises a first reference microarray experiment, and a second reference microarray experiment that is a nominal repeat of said first reference microarray experiment;

(b) determining, for each paired differential microarray experiment in said plurality of paired differential microarray experiments, an amount of change in expression level of said

cellular constituent between the second microarray experiment and the first microarray experiment using said error distribution statistic; and

(c) determining said probability that said expression level of said cellular constituent in said plurality of paired differential microarray experiments is altered by said perturbation by combining, for each paired differential microarray experiment in said plurality of paired differential microarray experiments, each amount of change in expression level of said cellular constituent determined in step (b) using a rank based method.

16. (Amended) The method of Claim 14 wherein said error distribution statistic is calculated according to a formula

$$\frac{(X - Y)}{\sqrt{\sigma_X^2 + \sigma_Y^2 + f^2(X^2 + Y^2)}}$$

where X represents an intensity of said cellular constituent in said first microarray experiment of said reference pair of microarray experiments, Y represents an intensity of said cellular constituent in said second microarray experiment of said reference pair of microarray experiments, σ_X^2 is a variance term for X that represents an additive error level in X, σ_Y^2 is a variance term for Y that represents an additive error level in Y, and f is a fractional multiplicative error level.

17. (Amended) The computer system of Claim 15 wherein said error distribution statistic is calculated according to a formula

$$\frac{(X - Y)}{\sqrt{\sigma_X^2 + \sigma_Y^2 + f^2(X^2 + Y^2)}}$$

where X represents an intensity of said cellular constituent in said first microarray experiment of said reference pair of microarray experiments, Y represents an intensity of said cellular constituent in said second microarray experiment of said reference pair of microarray experiments, σ_X^2 is a variance term for X that represents an additive error level in X, σ_Y^2 is a variance term for Y that represents an additive error level in Y, and f is a fractional multiplicative error level.

18. (Amended) The method of Claim 16 wherein said rank based method comprises determining a rank for said amount of change in expression level of said cellular constituent between said second microarray experiment and said first microarray experiment of said paired differential microarray experiment in relation to all cellular constituent measurements in said plurality of paired differential microarray experiments using said error distribution statistic.

19. (Amended) The computer system of Claim 17 wherein said rank based method comprises determining a rank for said amount of change in expression level of said cellular constituent between said second microarray experiment and said first microarray experiment of said paired differential microarray experiment in relation to all cellular constituent measurements in said plurality of paired differential microarray experiments using said error distribution statistic.

20. (Amended) The method of Claim 14 wherein said rank based method determines a probability that said cellular constituent is up-regulated in response to a perturbation.

21. (Amended) The computer system of Claim 15 wherein said rank based method determines a probability that said cellular constituent is up-regulated in response to a perturbation.

22. (Amended) The method of Claim 14 wherein said rank based method comprises computing

$$P(H_0^+)=\prod_i P_i$$

where P_i is the percentile rank of the expression of said cellular constituent in the i^{th} pair of paired differential microarray experiments in said plurality of paired differential microarray experiments, and $P(H_0^+)$ is the chance that said cellular constituent is not up-regulated in said plurality of paired differential microarray experiments.

23. (Amended) The method of Claim 14 wherein said rank based method determines a probability that said cellular constituent is down-regulated in response to said perturbation.

24. (Amended) The method of Claim 14 wherein said rank based method comprises computing

$$P(H_0^-) = \prod_i (1 - P_i)$$

where P_i is the percentile rank of the expression of said cellular constituent in the i^{th} pair of paired differential microarray experiments in said plurality of paired differential microarray experiments, and $P(H_0^-)$ is the chance that said cellular constituent is not up-regulated in said plurality of paired differential microarray experiments.

25. (Amended) The method of Claim 14 wherein each paired differential microarray experiment in said plurality of paired differential microarray experiments is a two-fluorophore microarray experiment wherein a first fluorophore represents said baseline state of said biological system and a second fluorophore, distinguishable from said first fluorophore, represents said perturbed state of said biological system.

26. (Amended) The method of Claim 14 wherein a single fluorophore is used in each said paired differential microarray experiments in said plurality of paired differential microarray experiments.

A9 27. (Amended) The method of Claim 14 wherein a first fluorophore is used in said first reference microarray experiment and a second fluorophore, distinguishable from said first fluorophore, is used in said second reference microarray experiment.

Please add the following claims:

A10 43. (New) The method of Claim 14 wherein said perturbed state of said first biological system is achieved by a method comprising exposing said first biological system, when representing said baseline state, to a pharmacological agent.

44. (New) The computer system of Claim 15 wherein said perturbed state of said first biological system is achieved by a method comprising exposing said first biological system, when representing said baseline state, to a pharmacological agent.

45. (New) The method of Claim 14 wherein said perturbed state of said first biological system is achieved by a method comprising exposing said first biological system, when representing said baseline state, to a drug candidate.

46. (New) The computer system of Claim 15 wherein said perturbed state of said first biological system is achieved by a method comprising exposing said first biological system, when representing said baseline state, to a drug candidate.

47. (New) The method of Claim 14 wherein said perturbed state of said first biological system is achieved by a method comprising introducing an exogenous gene into said first biological system.

48. (New) The computer system of Claim 15 wherein said perturbed state of said first biological system is achieved by a method comprising introducing an exogenous gene into said first biological system.

49. (New) The method of Claim 14 wherein said perturbed state of said first biological system is achieved by a method comprising deleting a gene from said first biological system.

50. (New) The computer system of Claim 15 wherein said perturbed state of said first biological system is achieved by a method comprising deleting a gene from said first biological system.

51. (New) The method of Claim 14 wherein said perturbed state of said first biological system is achieved by a method comprising changing a culture condition of said first biological system.

52. (New) The computer system of Claim 15 wherein said perturbed state of said first biological system is achieved by a method comprising changing a culture condition of said first biological system.

53. (New) The method of Claim 14 wherein said perturbed state of said first biological system is due to the onset of a disease in said first biological system.

54. (New) The computer system of Claim 15 wherein said perturbed state of said first biological system is due to the onset of a disease in said first biological system.

55. (New) The method of Claim 14 wherein said first biological system is a cell line, a cell culture, a tissue sample, an organ, or a multicellular organism.

56. (New) The computer system of Claim 15 wherein said first biological system is a cell line, a cell culture, a tissue sample, an organ, or a multicellular organism.

57. (New) The method of Claim 14 wherein said first biological system is a mammal.

58. (New) The computer system of Claim 15 wherein said first biological system is a mammal.

59. (New) The method of Claim 14 wherein said first biological system is a *Homo sapien*.

60. (New) The computer system of Claim 15 wherein said first biological system is a *Homo sapien*.

61. (New) The method of Claim 14 wherein said first biological system is a yeast that is substantially isogenic to *Saccharomyces cerevisia*.

62. (New) The computer system of Claim 15 wherein said first biological system is a yeast that is substantially isogenic to *Saccharomyces cerevisia*.

63. (New) The method of Claim 14 wherein said baseline state represents the wild-type state of said first biological system.

64. (New) The computer system of Claim 15 wherein said baseline state represents the wild-type state of said first biological system.

65. (New) The method of Claim 14 wherein said baseline state represents a different perturbed state of said first biological system.

66. (New) The computer system of Claim 15 wherein said baseline state represents a different perturbed state of said first biological system.

67. (New) The method of Claim 14 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least fifty percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

68. (New) The computer system of Claim 15 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least fifty percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

69. (New) The method of Claim 14 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least seventy-five percent of the genes in the genome of said first

biological system, and wherein said first biological system is a cell or a multicellular organism.

70. (New) The computer system of Claim 15 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least seventy-five percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

71. (New) The method of Claim 14 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least eighty-five percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

72. (New) The computer system of Claim 15 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least eighty-five percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

73. (New) The method of Claim 14 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least ninety percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

74. (New) The computer system of Claim 15 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray

experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least ninety percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

75. (New) The method of Claim 14 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least ninety-nine percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

76. (New) The computer system of Claim 15 wherein each said first microarray experiment and each said second microarray experiment in each paired differential microarray experiment in said plurality of paired differential microarray experiments uses a microarray having binding sites corresponding to at least ninety-nine percent of the genes in the genome of said first biological system, and wherein said first biological system is a cell or a multicellular organism.

77. (New) The method of claim 25 wherein said first fluorophore and said second fluorophore are selected from the group consisting of Cy2-deoxynucleotide triphosphate, Cy3-deoxynucleotide triphosphate, Cy3.5-deoxynucleotide triphosphate, Cy5-deoxynucleotide triphosphate, Cy5.5-deoxynucleotide triphosphate, Cy7-deoxynucleotide triphosphate, fluorescein, lissamine, phycoerythrin, and rhodamine.

78. (New) The method of claim 26 wherein said single fluorophore is selected from the group consisting of Cy2-deoxynucleotide triphosphate, Cy3-deoxynucleotide triphosphate, Cy3.5-deoxynucleotide triphosphate, Cy5-deoxynucleotide triphosphate, Cy5.5-deoxynucleotide triphosphate, Cy7-deoxynucleotide triphosphate, fluorescein, lissamine, phycoerythrin, and rhodamine.

79. (New) The computer system of Claim 15 wherein each paired differential microarray experiment in said plurality of paired differential microarray experiments is a two-fluorophore microarray experiment wherein a first fluorophore represents said baseline state of said first biological system and a second fluorophore, distinguishable from said first fluorophore, represents said perturbed state of said first biological system.

80. (New) The computer system of claim 79 wherein said first fluorophore and said second fluorophore are selected from the group consisting of Cy2-deoxynucleotide triphosphate, Cy3-deoxynucleotide triphosphate, Cy3.5-deoxynucleotide triphosphate, Cy5-deoxynucleotide triphosphate, Cy5.5-deoxynucleotide triphosphate, Cy7-deoxynucleotide triphosphate, fluorescein, lissamine, phycoerythrin, and rhodamine.

81. (New) The computer system of Claim 15 wherein a single fluorophore is used in said paired differential microarray experiments.

82. (New) The computer system of claim 81 wherein said single fluorophore is selected from the group consisting of Cy2-deoxynucleotide triphosphate, Cy3-deoxynucleotide triphosphate, Cy3.5-deoxynucleotide triphosphate, Cy5-deoxynucleotide triphosphate, Cy5.5-deoxynucleotide triphosphate, Cy7-deoxynucleotide triphosphate, fluorescein, lissamine, phycoerythrin, and rhodamine.

83. (New) The method of Claim 14 wherein said intensity independent statistic comprises the expression:

$$\frac{(X-Y)}{\sqrt{\sigma_X^2+\sigma_Y^2+f^2(X^2+Y^2)}}$$

where X represents an intensity of said cellular constituent in said first microarray experiment of said reference pair of microarray experiments, Y represents an intensity of said cellular constituent in said second microarray experiment of said reference pair of microarray experiments, σ_X^2 is a variance term for X that represents an additive error level in X, σ_Y^2 is a variance term for Y that represents an additive error level in Y, and f is a fractional multiplicative error level, and

said amount of change in expression level of said cellular constituent between the second microarray experiment and the first microarray experiment is determined using said error distribution statistic by a method comprising:

generating intensity independent contour lines using the denominator of said intensity independent statistic; and

determining the contour level of said change in expression level of said cellular constituent between the second microarray experiment and the first microarray experiment.

84. (New) The method of claim 83, wherein said intensity independent contour lines are gridded at a value selected from the group consisting of ±0.25 standard deviations, ±0.5 standard deviations, ±1 standard deviations, and ±2 standard deviations.

85. (New) The computer system of Claim15 wherein said intensity independent statistic comprises the expression:

$$\frac{(X-Y)}{\sqrt{\sigma_X^2+\sigma_Y^2+f^2(X^2+Y^2)}}$$

where X represents an intensity of said cellular constituent in said first microarray experiment of said reference pair of microarray experiments, Y represents an intensity of said cellular constituent in said second microarray experiment of said reference pair of microarray experiments, σ_X^2 is a variance term for X that represents an additive error level in X, σ_Y^2 is a variance term for Y that represents an additive error level in Y, and f is a fractional multiplicative error level, and

said amount of change in expression level of said cellular constituent between the second microarray experiment and the first microarray experiment is determined using said error distribution statistic by a method comprising:

generating intensity independent contour lines using the denominator of said intensity independent statistic; and

determining the contour level of said change in expression level of said cellular constituent between the second microarray experiment and the first microarray experiment.

86. (New) The method of claim 85, wherein said intensity independent contour lines are gridded at a value selected from the group consisting of ±0.25 standard deviations, ±0.5 standard deviations, ±1 standard deviations, and ±2 standard deviations.

87. (New) The method of Claim 14 wherein a radioactive label is used in each said paired differential microarray experiment in said plurality of paired differential microarray experiments.

88. (New) The method of Claim 14 wherein a first radioactive label represents a baseline state of said first biological system in each paired differential microarray experiment in said plurality of paired differential microarray experiments, and a second radioactive label represents a perturbed state of said first biological system in each paired differential microarray experiment in said plurality of paired differential microarray experiments, and wherein said first and second radioactive label have distinct emission spectra.

89. (New) The computer system of Claim 15 wherein a radioactive label is used in each said paired differential microarray experiment in said plurality of differential microarray experiments.

90. (New) The computer system of Claim 15 wherein a first radioactive label represents a baseline state of said first biological system in each paired differential microarray experiment in said plurality of paired differential microarray experiments, and a second radioactive label represents a perturbed state of said first biological system in each paired differential microarray experiment in said plurality of paired differential microarray experiments, and wherein said first and second radioactive label have distinct emission spectra.

91. (New) The computer system of Claim 21 wherein said rank based method comprises computing

$$P(H_0^+)=\prod_i P_i$$

where P_i is the percentile rank of the expression of said cellular constituent in the i^{th} pair of paired differential microarray experiments in said plurality of paired differential microarray

experiments, and $P(H_0^+)$ is the chance that said cellular constituent is not up-regulated in said plurality of paired differential microarray experiments.

92. (Amended) The computer system of Claim 15 wherein said rank based method determines a probability that said cellular constituent is down-regulated in response to a perturbation.

93. (New) The computer system of Claim 92 wherein said rank based method comprises computing

$$P(H_0^-) = \prod_i (1 - P_i)$$

where P_i is the percentile rank of the expression of said cellular constituent in the i^{th} pair of paired differential microarray experiments in said plurality of paired differential microarray experiments, and $P(H_0^-)$ is the chance that said cellular constituent is not up-regulated in said plurality of paired differential microarray experiments.

94. (New) The method of claim 14 further comprising, prior to step (a), performing each said paired differential microarray experiment in said plurality of paired differential microarray experiments to obtain measurements of the expression level of each cellular constituent in said set of cellular constituents.